

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Early life bereavement and childhood cancer: a nationwide follow-up study in two countries
AUTHORS	Momen, Natalie; Olsen, Jørn; Gissler, M; Cnattingius, Sven; Li, Jiong

VERSION 1 - REVIEW

REVIEWER	Terracini, Benedetto S. Giovanni Hospital and University of Torino
REVIEW RETURNED	25-Mar-2013

GENERAL COMMENTS	<p>This is a very interesting paper. By and large methods are correct and conclusions are reliable. It provides evidence that bereavement in early life may be causally associated to childhood cancer.</p> <p>The paper should be accepted for publication with minor revisions.</p> <p>Authors should expand on the control of potential confounders. Children in the exposed cohort were more likely to have had low birth weight, to be of higher birth order and to be born to older mothers, of Nordic origin, with lower education levels and more often reporting smoking during pregnancy. However, hazard ratios reported in Tables 2 and 3 were only adjusted for maternal age and parity. According to Table 1, the distribution of maternal country of origin (Nordic/non Nordic) and maternal education (an indicator of social class, as well as tobacco smoking) differed between the exposed and the non exposed groups. Why did authors ignore these potential confounders in the adjusted analyses?</p> <p>Hazard ratios in Tables 2 and 3 are not adjusted for weight at birth. Truly, the proportion of newborns under 2500 g was similar in the two groups. However, mothers' lifestyle is relevant to birth weight and may be relevant also to the probability of having a death in the family. Perhaps a description of the analyses stratified for birth weight could be useful (possibly three or more strata).</p> <p>In the discussion, authors should point out that the inclusion of separate analyses on tumours of the Central Nervous System was not based on any a priori hypothesis. Thus, although statistical estimates of hazard ratios are similar for CNS tumours and leukaemias, any causal inference for the former should be more cautious than for the latter. The additional analyses in which children were moved to the exposed group 3 months after the event leading to bereavement are appropriate. One could wonder whether such a lag could not be too short.</p>
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REVIEWER	Wolchik, Sharlene Arizona State University
REVIEW RETURNED	04-Apr-2013

GENERAL COMMENTS	<p>This manuscript examined the association between bereavement and childhood cancer. There are several strengths of the manuscript. First, it examines an important but understudied topic. Second, the data sets are two national registers and so the sample is large and representative. Third, the analyses are prospective. Fourth, the rate of retention was exceptional. Fifth, the authors examined whether risk varied by death of close vs. distant relative, sudden vs. other death and timing of exposure. However, there are some problems that limit the scientific contribution of the manuscript.</p> <p>The most important concern involves the analyses. It is not clear why hazard ratios rather than odds ratios were computed given that the outcome measure was presence or absence of cancer (or a specific type of cancer). Also, additional information about the kinds of tests that were conducted to examine differences between the exposure and nonexposed groups on demographic characteristics is needed. The p levels of these comparisons should be included in Table 1. Further, there is a lack of clarity and consistency about how differences on these demographic variables were handled in the analyses. Some of these factors were adjusted (maternal age, parity and multiplicity). Others were examined by stratification (sex, country, birth weight, gestational age). Others were adjusted for in sub-analyses (maternal education, smoking during pregnancy). Apgar score differences between the exposed and unexposed groups do not seem to have been included in the analyses. Further, there is some confusion about how country was handled. In Table 2, there is a note that country was controlled. In the text, it is noted that stratification by country analyses were conducted. It is unclear why all the variables on which significant differences occurred between the exposed and nonexposed groups were not treated in the same way. Including these variables as covariates would allow the authors to have more confidence in the link they make between bereavement and childhood cancer.</p> <p>There are a couple of places where additional information would be helpful. For example, it would be important to define "more distant" relative. It would also be useful to provide a rationale for the subgroup analyses.</p>
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VERSION 1 – AUTHOR RESPONSE

Reviewer: Benadetto Terracini
S. Giovanni Hospital and University of Torino

Comment:

This is a very interesting paper. By and large methods are correct and conclusions are reliable. It provides evidence that bereavement in early life may be causally associated to childhood cancer.

The paper should be accepted for publication with minor revisions.

Response:

Thank you for the comment. We have revised the manuscript accordingly.

Comment:

Authors should expand on the control of potential confounders. Children in the exposed cohort were more likely to have had low birth weight, to be of higher birth order and to be born to older mothers, of Nordic origin, with lower education levels and more often reporting smoking during pregnancy. However, hazard ratios reported in Tables 2 and 3 were only adjusted for maternal age and parity. According to Table 1, the distribution of maternal country of origin (Nordic/non Nordic) and maternal education (an indicator of social class, as well as tobacco smoking) differed between the exposed and the non exposed groups. Why did authors ignore these potential confounders in the adjusted analyses?

Response:

As mentioned in the paper, the variables we adjusted for were selected a priori based on the literature, as has been suggested in recent literature. Maternal education and tobacco smoking which (as the reviewer points out) also differed between the two groups, were adjusted for in sub-analyses. The reason they were included in subanalyses, and not the main analysis, was because of the relatively high proportion of missing values these variables had; this was partly because, as mentioned in the text, they were not recorded for the entire study period (in Denmark, maternal education was available only from 1980; and maternal smoking during pregnancy was available only from 1991 in Denmark and from 1983 in Sweden). We have added to the methods section to clarify this (page 9, paragraph 1).

Comment:

Hazard ratios in Tables 2 and 3 are not adjusted for weight at birth. Truly, the proportion of newborns under 2500 g was similar in the two groups. However, mothers' lifestyle is relevant to birth weight and may be relevant also to the probability of having a death in the family. Perhaps a description of the analyses stratified for birth weight could be useful (possibly three or more strata).

Response:

As suggested by the reviewer we have carried out the stratification using three strata instead of two – the estimates for each strata did not differ significantly (<2500g: HR 1.17, 95% CI 0.88-1.56; 2500-4000kg: HR 1.07, 95% CI 0.96-1.12; ≥4000kg: HR 1.23, 95% CI 1.07-1.42), the conclusion of this analysis has been stated in the paper (page 11, paragraph 2).

Comment:

In the discussion, authors should point out that the inclusion of separate analyses on tumours of the Central Nervous System was not based on any a priori hypothesis. Thus, although statistical estimates of hazard ratios are similar for CNS tumours and leukaemias, any causal inference for the former should be more cautious than for the latter.

Response:

As the reviewer states, we included CNS tumours along with the other more common childhood cancers, although our expectation was that any associations would be seen for hormone or immune related cancers. As suggested, we have added to the discussion, where possible reasons for the observed associations are discussed. We highlight that although CNS tumours were not initially hypothesised to be increased among the exposed (page 15, paragraph 1), leukaemias and CNS

tumours are two childhood cancers which have been suggested to be initiated in utero – bereavement could provide a necessary “second hit” for these cancers, which could explain the small association we saw.

Comment:

The additional analyses in which children were moved to the exposed group 3 months after the event leading to bereavement are appropriate. One could wonder whether such a lag could not be too short.

Response:

We agree that there is uncertainty over the appropriate length of lag; to highlight this uncertainty, we have added to the discussion about using the lag period in the additional analyses. We also re-ran the main analysis using a lag period of 1 year and the results did not differ significantly (HR 1.08, 95% CI 1.01-1.16) – we have added this to the results (page 13, paragraph 3).

Reviewer: Sharlene Wolchik
Arizona State University

Comment:

This manuscript examined the association between bereavement and childhood cancer. There are several strengths of the manuscript. First, it examines an important but understudied topic. Second, the data sets are two national registers and so the sample is large and representative. Third, the analyses are prospective. Fourth, the rate of retention was exceptional. Fifth, the authors examined whether risk varied by death of close vs. distant relative, sudden vs. other death and timing of exposure. However, there are some problems that limit the scientific contribution of the manuscript.

Response:

Thank you for your comments. We have revised the manuscript and provided more detail where needed.

Comment:

The most important concern involves the analyses. It is not clear why hazard ratios rather than odds ratios were computed given that the outcome measure was presence or absence of cancer (or a specific type of cancer).

Response:

We are interested in comparing the risk of cancer between the exposed group and unexposed group, using time to event data. Our follow-up period is from birth to 14 years of age, thus for some study participants we have censored data. That is, the “time to event” for those individuals who have not been diagnosed with cancer is censored by the end of study; those who died or emigrated before the end of the study are censored. Such data can be handled by Cox regression, not logistic regression.

Comment:

Also, additional information about the kinds of tests that were conducted to examine differences between the exposure and nonexposed groups on demographic characteristics is needed. The p levels of these comparisons should be included in Table 1.

Response:

P values from the chi squared tests have been included in Table 1 as requested.

Comment:

Further, there is a lack of clarity and consistency about how differences on these demographic variables were handled in the analyses. Some of these factors were adjusted (maternal age, parity and multiplicity). Others were examined by stratification (sex, country, birth weight, gestational age). Others were adjusted for in sub-analyses (maternal education, smoking during pregnancy). Apgar score differences between the exposed and unexposed groups do not seem to have been included in the analyses. Further, there is some confusion about how country was handled. In Table 2, there is a note that country was controlled. In the text, it is noted that stratification by country analyses were conducted. It is unclear why all the variables on which significant differences occurred between the exposed and nonexposed groups were not treated in the same way. Including these variables as covariates would allow the authors to have more confidence in the link they make between bereavement and childhood cancer.

Response:

As the reviewer states, maternal age, parity and multiplicity were adjusted for, as was country. The subanalyses with maternal education and smoking were carried out as we considered these to be potential confounders, but (as mentioned above) there were a relatively high proportion of missing values due to this data being available for a limited period only.

Stratified analyses were carried out for variables which we did not believe to be confounders of the association between postnatal bereavement and childhood cancer, but we thought could be effect modifiers - for example, children who had had a low birth weight might be more vulnerable to exposures in early postnatal life and therefore we wanted to see if they were affected differently following the death of a relative compared to children who had had a normal birth weight. We have edited the text to clarify and explain the rationale for this more clearly (page 9, paragraph 1).

Following the reviewer's suggestion, we repeated the analysis stratifying by Apgar score – the confidence intervals suggest there is not a difference between the groups (Apgar score 7-10: HR 1.07, 95% CI 1.00-1.14; Apgar score <7: HR 1.25, 95% CI 0.69-2.25). We have mentioned this in the text (page 11, paragraph 2).

Comment:

There are a couple of places where additional information would be helpful. For example, it would be important to define "more distant" relative. It would also be useful to provide a rationale for the subgroup analyses.

Response:

We have added an explanation of 'more distant' relative to the methods section (page 8, paragraph 3) and the reason for the subgroup analyses to the methods sections of the paper to address this comment (page 9, paragraph 1).

VERSION 2 – REVIEW

REVIEWER	Sharlene A. Wolchik Psychology Department Arizona State University Tempe, AZ 85287 U.S. I do not have any competing interests.
REVIEW RETURNED	29-Apr-2013

GENERAL COMMENTS	The authors were responsive to the reviewers' concerns and have made all the necessary revisions.
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